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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,017	08/02/2001	Gregory S. Hamilton	AR762-XXA	7616
29728	7590	12/28/2005	EXAMINER	
GUILFORD PHARMACEUTICALS C/O FOLEY & LARDNER LLP 3000 K STREET, NW WASHINGTON, DC 20007-5143			CHANG, CELIA C	
			ART UNIT	PAPER NUMBER
			1625	

DATE MAILED: 12/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/920,017	Applicant(s) HAMILTON ET AL.
	Examiner Celia Chang	Art Unit 1625
	-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --	
Period for Reply <p>A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.</p> <ul style="list-style-type: none"> - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b). 		
Status <p>1)<input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>12 December 2003</u>.</p> <p>2a)<input type="checkbox"/> This action is FINAL. 2b)<input checked="" type="checkbox"/> This action is non-final.</p> <p>3)<input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i>, 1935 C.D. 11, 453 O.G. 213.</p>		
Disposition of Claims <p>4)<input checked="" type="checkbox"/> Claim(s) <u>1-3,5-7,9-11 and 13</u> is/are pending in the application.</p> <p>4a) Of the above claim(s) _____ is/are withdrawn from consideration.</p> <p>5)<input type="checkbox"/> Claim(s) _____ is/are allowed.</p> <p>6)<input checked="" type="checkbox"/> Claim(s) <u>1-3,5-7,9-11 and 13</u> is/are rejected.</p> <p>7)<input type="checkbox"/> Claim(s) _____ is/are objected to.</p> <p>8)<input type="checkbox"/> Claim(s) _____ are subject to restriction and/or election requirement.</p>		
Application Papers <p>9)<input type="checkbox"/> The specification is objected to by the Examiner.</p> <p>10)<input type="checkbox"/> The drawing(s) filed on _____ is/are: a)<input type="checkbox"/> accepted or b)<input type="checkbox"/> objected to by the Examiner.</p> <p style="margin-left: 20px;">Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).</p> <p style="margin-left: 20px;">Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).</p> <p>11)<input type="checkbox"/> The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.</p>		
Priority under 35 U.S.C. § 119 <p>12)<input type="checkbox"/> Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).</p> <p>a)<input type="checkbox"/> All b)<input type="checkbox"/> Some * c)<input type="checkbox"/> None of:</p> <p>1.<input type="checkbox"/> Certified copies of the priority documents have been received.</p> <p>2.<input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____.</p> <p>3.<input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).</p> <p>* See the attached detailed Office action for a list of the certified copies not received.</p>		
Attachment(s) <p>1)<input checked="" type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2)<input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3)<input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.</p> <p>4)<input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.</p> <p>5)<input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</p> <p>6)<input type="checkbox"/> Other: _____.</p>		

DETAILED ACTION

1. In view of the newly available pre-grant reference, the finality of the rejection dated May 30, 2003 have been withdrawn and the prosecution is reopened. The brief filed by applicants dated Dec. 2, 2003 is considered a response to the rejection of May 30, 2003 now made non-final.

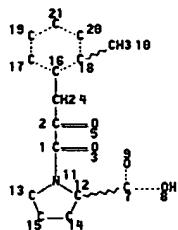
Claims 1-3, 5-7, 9-11 and 13 are pending.

2. The rejection of claims 1, 2, 5, 6, 10 and 13 under 35 USC 112 second paragraph is maintained for reasons of record.

Applicants argued that the claims are not indefinite because if the meaning of the claims are discernible, however confusing the task may be in discerning it, it is definite (see brief p. 6-8). In addition, claims 5 and 13 incorporated compounds by reference is not improper.

It is noted that a question was raised by giving examples from prior art cited by applicants or of record and a “discernment” on whether these compounds are “in” or “out” of the claims can not be ascertained. The self conflicting evidence of the confusing in discerning what is the meets and bounds of the claim can be found for example (examples only, not an exhausted listing), in claim 1, the scope of R1 is “C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, aryl, heteroaryl, carbocycle, or heterocycle;”. The first proviso said “provided that when D is a bond an R2 is COOH, then R1 is not C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₅-C₇ cycloalkyl, C₅-C₇ cycloalkenyl, phenylamine, 2-(3,4-dichlorophenyl)ethyl, hydroxyl, ethoxy, benzyl or Ar1 wherein Ar1 is 1-naphthyl, 2-naphthyl, 2-indolyl, 3-indolyl, 2-furyl, 3-fryl, 2-thiazole, 2-thienyl, 3-thienyl, 1-pyridyl, 2-pyridyl, 4-pyridyl or phenyl and wherein said alkyl, alkenyl, cycloalkyl, cycloalkenyl or Ar1 is optionally substituted with one of more substituents selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C₁-C₉ straight or branched chain alkyl, C₂-C₉ straight or branched chain alkenyl, C₁-C₄ alkoxy, C₂-C₄ akenyloxy, phenoxy, benzyloxy, COOH, and amino”. Please note that the R1 moiety defined by claim 1 does not allow substitution yet the proviso disclaimed that R1 can be benzyl. So does the prior compound of CA 121:887 proviso

out or not, can it be used to reject a species of claim 5, named in compound 45 for which the following structure is delineated.



This is an one methyl addition of the prior art compound which is structurally *prima facie*, but the base claim proviso this compound for which not antecedent basis of the R1 moiety can be found for this proviso. By definition of the R1 moieties of the base claim, since the alkyl moiety can not be substituted, the compound when R1 is benzyl (see CA 121:887 structural delineation, CA 121:87 corresponding to reference BH recited on page 2 of the 1449 dated 12/12/02) is not within the “meets and bounds” of the claim. Yet the proviso placed it back into the claim by proviso “benzyl” out and supported it with a species claim (see claim 5, compound 45). This is very confusing as to “what” is the meets or bounds of the claim when self conflicting meets and bounds are incorporated in the claims. The many self conflicting scope between the definition of the Markush elements and the proviso elements will not be exhausted listed. Applicants have been advised that second paragraph require applicants to “particularly point” to “what” is applicants’ invention, not by three pages of proviso noting out what is “not” applicants invention.

Applicants argument with respect to carbocycle or heterocycle containing any combination of CH2, O,S or N” reading on phenyl is self conflicting. When a “carbocycle containing only CH2, how can it be phenyl? The second paragraph rejection based on ambiguity and what is being claimed is very clear since even the attorney does not know what this term includes.

The rejection of claims 5 and 13 are proper based on the decision of *Ex parte Fressola*. Applicants offered no good reason that why the compounds of table I, II or III which can be delineated and named, have any unusual difficulty in properly naming such in the claim but have to be incorporated by reference. As it was stated clearly by Fressola, claims should *stand on its own* without any ambiguity or reference from the specification unless in very limited situation that the nature of the subject matter can not be “named”. Chemical compounds have the

standard IUPAC name, thus, there is no reason why such names can not be incorporated into the claim but have to be referred to from the specification.

3. The rejection of claims 1-2, 8-9 over Gold, Burbaum or Bycroft under 35 USC 102(b) is maintained. Please note that anticipation was found over the non-elected subject matter which evidenced the propriety of the restriction. Further, according to MPEP §803.02 for Markush practice it was clearly instructed that when the search for a Markush type claim is extend to the non-elected species, if prior art is then found that **anticipates** or renders obvious the Markush-type claim with respect to a *non-elected species*, the Markush type claim should be rejected and claims to the nonelected subject matter held withdrawn. Therefore, the rejection and recommendation of deletion of nonelected subject matter from the Markush claims are proper.

Applicants provided no rational on why the Markush practice was improper when the procedure is exactly according to MPEP. There is no good reason why when **anticipatory** species of the non-elected subject matter was clearly made instead of withdrawing the non-elected invention per procedure of MPEP, applicants should demand explanation on obviousness since anticipation is the epitome of obviousness.

4. Claims 1-2, and 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The term carboxylic acid or carboxylic acid isostere of the claims broadly included many discovered chemical moieties for which antecedent basis or description are lacking in the specification. One example is given that the carboxylic acid isostere can be a 1,3,4-oxadiazole such as described in Biagi et al. CA 114:122192 or Polanski et al. CA 135:272922, for which no description was found in the specification but encompassed broadly by the term carboxylic acid isostere. Therefore, for the broad scope encompassing 1,3,4-oxadiazole, applicants are entitled to no benefit of the application date nor any priority date (see p.25 specification).

Further, for any new isostere or bioisostere of the carboxylic acid discovered after the filing date or in the future, the specification lacks any antecedent basis or description to support the scope of the claim encompassing such structure moiety.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

(g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Claims 1-2, 9-10 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Brumby et al. US 6,284,779.

See example 2, col. 12, or claim 5 first compound, col 13.

Applicants argued that the rejection was made based on conclusory statements or was resolved on the subjective belief of the examiner. This is entirely erroneous. Please note that for the subject matter of claims 1-2, 9-10 when the carboxylic acid isostere is a 1,3,4-oxadiazole, applicants' specification is deficient in providing description thus is entitled to no benefit of application date or priority date. The Brumby '779 reference name the compound in example 2 or claim 5 and a commercial ChemDraw can give the structural delineation for the attorney. Therefore, the rejection was based on "real material" described and enabled in the reference. No conclusion nor belief needs to be made for the rejection.

Because the US 6,284,779 has a "different" inventorship and claimed an anticipatory compound of the claims, a rejection under 102(f) or (g) are also applicable.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 5-7, 9-11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamilton US 5,859,031, US 5,945,441, US 6177,455, US 6,291,510 in view of Silverman or Bungaard further in view of Li et al. US 5,801,187, Li et al. US 6,218,544 (all references recited on PTO 1449 or 892) and Patani.

Determination of the scope and content of the prior art (MPEP §2141.01)

Hamilton '031, '441, '445, '510 disclosed pyrrolidinyl compounds with 1-dioxolyl substitution and 2- carboxylic ester and their compositions which have identical utility as the instantly claims i.e. neurotrophic/immunophillin inhibitors.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Hamilton '031, '441, '445, '510 disclosed all the elements of the claims **except** the compounds are in form of an ester of the instant carboxylic acid or carboxylic acid isostere. Bungaard taught that ester is a "prodrug" of free carboxylic acid compounds since naturally, under physiological conditions, the ester will be hydrolyzed to acid by esterases which can be found in the blood, liver and other organs or tissues (see Bungaard p.3-4 para bridging) while Silverman taught the same concept further taught the same approach can be extend to sulfate or phosphate esters (see p.356) and the modification of the ester moiety to increase the hydrolyzation rate (see p.357). Li et al. '187 and '544 evidenced that the general approach taught by Bungaard or Silverman is applicable to the field of small molecules having neurotrophic/immunophillin inhibitors analogous to the instantly claimed compounds. Patani et al. taught that the replacement of a functional group in a drug with its bioisoster is a rational approach to artisan in the field (see whole article especially page 1 and p.3168-3169)

Finding of prima facie obviousness—rational and motivation (MPEP §2142-2143)

One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the prodrug and how such prodrug functions physiologically in the possession of artisan in the field. One skilled in the art in possession of the Hamilton '031, '441, '445, '510 is tantamount to in possession of the instant claims **because** the mechanism of how a prodrug functions through the drug can not be separated from the drug per se. Further, it is evidenced in the art that both the free carboxylic acid (see Li '544, col. 14, claim 1) and the ester (see Li '187, col. 13-14 claims 1-12) functions analogously. No evidence in the record indicated that the esters of Hamilton '031, '441, '445, '510 should not function in physiological conditions according to common knowledge of the art as taught by Bungaard or Silverman. Therefore, to the extend that the claims are drawn to carboxylic acid a case of prima facie obviousness is the innate nature of the drug metabolism. To the extend that the claimed scope being drawn to an isostere of carboxylic acid such as found in claim 3, the replacement of

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a carboxylic acid functional group with its bioisostere (see Patani p.3168-3169) is a rational approach in drug modification conventional to one having ordinary skill. The motivation, the enablement and the reasonable expectation of maintaining acitivity are conventionally employed in a rational manner in the field (see Patani whole article).

7. Claims 1-3, 5-7, 9-11, 13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 18 of U.S. Patent No. 5,859,031, claim 4, of U. S. Patent no. 6,291,510 in view of Silverman or Bungaard further in view of claims 1-8 of Li et al. US 5,801,187, claim 1 of Li et al. US 6,218,544 and Patani.

The same rational as section 6 of finding the claims *prima facie* obvious is applicable and hereby incorporated by reference.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-3, 5-7, 9-11, 13 are rejected under 35 U.S.C. 102(e) or (f) as being clearly anticipated by US 2004/0186098.

See p.62-66 identical compounds as those of tables I, II or III of the instant application.

Please note that the US 2004/0186098 has a provisional date prior to the instant provisional date and has an entirely different inventive entity. However, the '098 application and the instant application share "one" common assignee.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f).

In addition, applicants should file affidavit showing that the copending applications are commonly own and subject to the same obligation of assignment at the time the invention was made and the US 2004/0186098 claims were derived from the material of the instant application thus establishing the first inventor for the claimed material (see MPEP 715.03

Failure to comply with this requirement will result in a holding of abandonment of this application.

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9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Celia Chang

Primary Examiner
Art Unit 1625

OACS/Chang